I. The Office Action

Applicant thanks the Examiner for withdrawal of previous rejections under 35 USC 112, second paragraph and four previously made rejections under 35 USC 103(a). Currently, the September 18, 2008 non-Final Office Action (the "Office Action"):

1. rejected claims 22-24, 28 and 36 under 35 U.S.C. 103(a);

2. rejected claims 25 and 37 under 35 U.S.C. 103(a); and

3. rejected claims 26-27 under 35 U.S.C. 103(a).

Applicant respectfully traverses these newly-made rejections.

II. Rejection of claims 22-24, 28 and 36 under 35 U.S.C. 103(a)

The Office Action rejected claims 22-24, 28 and 36 under 35 U.S.C. 103(a) as being unpatentable over Pearce et al. (USP 6087327) in view of Moher et al (USP 5591767) and in further view of Singer et al. (Acad Emerg Med 1998 Nov;5(11):1051-6 (abstract only). Applicants respectfully traverse this rejection.

In discussing the primary reference cited in this obviousness rejection of clams 22-24, 28 and 36, the Office Action states, in part, that Pearce et al., "...teach that the transdermal delivery of botulinum toxin comprising a depot (botulinum toxin in the dried state)...(Column 9)". Respectfully, it is pointed out that Pearce et al. in fact does not disclose the transdermal delivery of botulinum toxin via a depot, but rather discloses "...implantation of a depot-type release modality..." (col. 9, line 15). Implantation of a depot-type release modality has no relation to transdermal delivery, but rather the implantation (i.e. insertion or embedding an object or a device surgically) of a drug delivery system. Thus Pearce et al. in fact does not "...teach that depots of the invention can be used in transdermal diffusion (column 9)" (Office Action, p.4 line 18-19), but rather that

the depots disclosed in Pearce et al. are *implanted* and thus have nothing to do with transdermal diffusion or administration.

This holding by the Office Action of the teachings of Pearce et al. is inaccurate and thus inapplicable to the instant claims. In fact, in taking the whole of Pearce et al. into consideration, it is noted that Pearce et al. does not teach the use of an enhancing agent, as presently recited in the instant claims. This is not surprising because, and as shown at col. 4, lines 1-9, it is stated that the compositions of Pearce et al. provide more localized, less widespread denervation, that is, the compositions and teachings of Pearce et al. go to minimizing the spread of botulinum toxin and resultant non-localized denervation. It is stated that this is advantageous because it will not expose a patient to the undesirable and non-specific side-effects caused by diffusion-dependent spreading of botulinum toxin admixtures.

Indeed and taking Pearce et al. as a whole, is it clear that one of the advantages of its admixed compositions is this limiting of the diffusion of the toxin from its point of administration. Thus one of ordinary skill in the art would not make the jump, let alone have a reasonable expectation of success, to move from these teachings in Pearce et al., in pursuit of diffusion-based methods that would be directed to achieving the opposite effect, that is, to references that are direct to achieving methods to facilitate (i.e. *enhance*) diffusion of botulinum toxin, even transdermally, once administered to a patient. This is *opposite* of the teachings and objectives of Pearce et al. Furthermore, this explains why there is no mention of permeation enhancers or transdermal patches, as presently claimed, and are not taught or suggested by Pearce et al. Thus the Office Action's turning to other references is suggested not by a reading of Pearce et al., but rather by a hindsight-cased reconstruction based upon the instant claims. It is respectfully noted that the Office Action must show that the combination of prior art would have provided one of ordinary skill in the art with a reasonable expectation of success. Both the suggestion and the reasonable expectation of success must be adequately founded in the prior art, and not in the instant application.

For example, Mohr et al. and its disclosure regarding transdermal patches would be properly considered/combined if, for example, one of ordinary skill in the art would be directed to/look to the use of transdermal/diffusion enhancers (which are not disclosed in Pearce et al.) and secondly one of ordinary skill in the art had a reasonable expectation of successful use of such enhancers with botulinum toxin admixtures. However, this is not the case. As discussed above, the introduction/consideration of diffusion enhancers does not comport with the disclosure of Pearce et al. which discloses the limited diffusion characteristics of its admixtures, and thus one of ordinary skill would not, based on Pearce et al., turn to Mohr et al. Secondly, a review of Mohr et al. reveals that there is not one mention of botulinum toxin, let alone toxin and its use in a transdermal patch. It is further noted that Mohr et al. does not disclose the method step of applying a fluid to a patient's skin, which then will solubilize the botulinum toxin provided in the dry state with this fluid applied to the patient's skin.

Thus, one is forced to ask, "What is the basis of the required expectation of success to be found in this combination, where Pearce et al. does not teach transdermal patches or diffusion enhancers, and Mohr et al. does not mention or suggest the use of botulinum toxins in the context of enhancers and transdermal patches?" It is respectfully asserted one of ordinary skill in the art would not have a reasonable expectation of success, since enhancers and transdermal patches are not found in Perace et al., and enabled use of botulinum toxin in the context of the disclosure of Mohr et al., is not to be found, thus a proper prima facie assertion of obviousness cannot be made. The inclusion of Singer et al. disclosure regarding cutaneous tape stripping fails to remedy these primary deficiencies/hurdles. As discussed in *KSR Int'l Co. v. Teleflex, Inc.*, 550 U.S. 398, 127 S. Ct. 1727, 82 U.S.P.Q.2d 1385, obviousness analysis must not be applied in a rigid or formulaic way, such that the TSM test can capture the important insight that a claimed invention is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art. Thus this rejection should be withdrawn.

III. Rejection of claims 25 and 37 under 35 U.S.C. 103(a)

The Office Action rejected claims 25 and37 under 35 U.S.C. 103(a) as being unpatentable over Pearce et al. in view of Moher et al. and Singer et al. and Mitragotri et al. (Science, Vol. 269, Aug. 11,1995) . Applicants respectfully traverse this rejection.

The improper combination of Pearce et al. in view of Moher et al and Singer et al. is discussed above, and the addition of Mitragotri et al. does not remedy the failure of the Office Action to make its asserted prima facie case of obviousness, as discussed above. The Office Action's forced combination of the opposite goals/teaching of Pearce et al. (an admixture of botulinum toxin and goal of limiting diffusion from point of administration) with the diffusion-facilitating disclosure of Mohr et al. relating to ketorolac tromethamine (a non-steroidal anti-inflammatory drug) and diffusion enhancers, as well the Office Action's failure to support/show, as evidenced by the prior art, why one of ordinary skill in the art would have a reasonable expectation of success of such a combination, is not remedied by the inclusion of disclosure related to ultrasound-mediated transdermal protein delivery. Mitragotri et al. discloses ultrasound-mediated transdermal protein delivery, and does not mention transdermal patches, botulinum toxin or steps as presently detailed in the pending claims. Thus, this rejection should be withdrawn.

IV. Rejection of claims 26-27 under 35 U.S.C. 103(a)

The Office Action rejected claims 26-27 under 35 U.S.C. 103(a) as being unpatentable over Pearce et al., Moher et al., Singer et al., Mitragotri et al. as applied above to claims 22-25, 28 and 36-37 and in further view of Yuzhakov et al. (USP 6565532). Applicants respectfully traverse this rejection.

The improper combination of Pearce et al., Moher et al., Singer et al. and the failure of Singer et al. to remedy this deficiency, as well as the addition of Mitragotri et al. to this improper combination is discussed above. The addition of Yuzhakov et al., further fails to remedy the Office Action's improper combination and does not support a proper prima facie case of obviousness. It is noted that

method steps recited in claim 22, where a fluid is applied to a patient's skin to which a transdermal patch (having the dry botulinum toxin and an enhancing agent) is applied in order to solubilize the dry botulinum toxin with the previously applied fluid, cannot be found in Yuzhakov et al. The missing steps are only provided for and found in the instant application and claims.

Furthermore, Applicant respectfully points out that is appears that the Office Action maintains in its rejection its misconstrued meaning of the term "polymers" in Yuzhakov et al. (please see Office Action, p. 11, lines 12-15) to mean an enhancing agent. This is simply incorrect, as a review of column 28 of Yuzhakov et al. shows that the term "polymers" (col. 28, line 63) is directed to and is part of a list of materials by which the "closed-loop system" and body-fluid sampling sensors, exemplified in Figures 30 and 31 of Yuzhakov et al., can be made of. The list of suitable material for construction of the "closed-loop system" includes diamond, bio-compatible metal, ceramics, polymers, polymer composites (col. 28, lines 60-65).

In this reference, botulinum toxin is mentioned in passing as part of a general list of "other types of skin structure modifiers can also be applied through the microneedle patch, including such ingredients as fat, collagen, botulinum toxin, fibril, silicones, hydrogels, elastomers, and colloids.", and certainly no distinction is made or provided by Yuzhakov et al. regarding providing botulinum toxin in a dried state in a transdermal patch, nor discloses or suggests any advantages provided by a method that utilizes the claimed configuration of fluid, botulinum toxin and enhancer, as claimed in the instant specification. Thus, the rejection should be withdrawn.

V. Conclusion

All issues raised in the Office Action have been addressed. Reconsideration and allowance of claims 22-28 and 36-37 is requested.

The Commissioner is hereby authorized to charge any fee(s) required or necessary for the filing, processing or entering of this paper or any of the enclosed papers and to refund any overpayment to deposit account 01-0885.

Respectfully submitted,

/Claude L. Nassif/

Date: March 10, 2008

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